# Significant reduction of red blood cell transfusion requirements by changing from double- to single-unit transfusion policy in patients receiving intensive chemotherapies or stem cell transplantation

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Abstract: Background. Traditionally, single-unit red blood cell (RBC) transfusions were believed to be insufficient to treat anemia, but recent data suggest that they may lead to a safe reduction of transfusion requirements. We tested this hypothesis by changing from double- to single-unit RBC transfusion policy. Design and Methods. We performed a retrospective cohort study in patients with hematological malignancies receiving intensive chemotherapy or hematopoietic stem cell transplantation. The major endpoints were the reduction in the total number of RBC units per therapy cycle and per day of aplasia. The study comprised 139 patients receiving 272 therapy cycles. A total of 2212 RBC units were administered in 1548 transfusions. Results and conclusions. During the double- and single-unit period one RBC unit was transfused in 25% and 84% of the cases and the median number of RBC units per transfusions was 2 and 1, respectively. Single-unit transfusion led to a 25% reduction of the RBC requirements per therapy cycle and 24% per aplasia day, but was not associated with a higher outpatient transfusion frequency. In multivariate analysis, single-unit transfusion resulted in reduction of 2.7 RBC units per treatment cycle (p=0.001). The pretransfusion hemoglobin levels were lower during the single-unit period (median 61g/L vs. 64g/L) and more transfusions were administered in patients with hemoglobin values 60gl/L (47% vs. 26%). Neither more severe bleedings nor platelet transfusions were recorded during the single-unit period and the overall survival was similar in both cohorts. Conclusions. Implementing a single-unit transfusion policy saves 25% of RBC units and thereby reduces the risks associated with allogeneic blood transfusions.

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# Significant reduction of red blood cell transfusion requirements by changing from double- to single-unit transfusion policy in patients receiving intensive chemotherapies or stem cell transplantation

*SHORT TITLE: Single-unit red blood cell transfusions*

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Key words: red blood cells, transfusion, single-unit, acute leukemia, hematopoietic stem cell transplantation.

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## Abstract

*Background*

Traditionally, single-unit red blood cell transfusions were believed to be insufficient to treat anemia, but recent data suggest that they may lead to a safe reduction of transfusion requirements. We tested this hypothesis by changing from double- to single-unit red blood cell transfusion policy.

*Design and methods*

We performed a retrospective cohort study in patients with hematological malignancies receiving intensive chemotherapy or hematopoietic stem cell transplantation. The major endpoints were the reduction in the total number of red blood cell units per therapy cycle and per day of aplasia. The study comprised 139 patients receiving 272 therapy cycles. A total of 2212 red blood cell units were administered in 1548 transfusions.

*Results*

During the double- and single-unit period one red blood cell unit was transfused in 25% and 84% of the cases and the median number of red blood cell units per transfusions was 2 and 1, respectively. Single-unit transfusion led to a 25% reduction of the red blood cell requirements per therapy cycle and 24% per aplasia day, but was not associated with a higher outpatient transfusion frequency. In multivariate analysis, single-unit transfusion resulted in reduction of 2.7 red blood cell units per treatment cycle ($p=0.001$). The pretransfusion hemoglobin levels were lower during the single-unit period (median 61g/L vs. 64g/L) and more transfusions were administered in patients with hemoglobin values ≤ 60gl/L (47% vs. 26%). Neither

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more severe bleedings nor platelet transfusions were recorded during the single-unit period and the overall survival was similar in both cohorts.

*Conclusions*

Implementing a single-unit transfusion policy saves 25% of red blood cell units and thereby reduces the risks associated with allogeneic blood transfusions.

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## Introduction

Single-unit red blood cell (RBC) transfusions were extensively criticized in the past. It was believed that RBC transfusions were useless if the transfusion requirements could be satisfied by infusion of one RBC unit and that patients were no more in need of the transfusion than their donors[1-3]. However, data on the risk or benefit of a single-unit transfusion strategy is scarce and most evidence derives from studies analyzing perioperative single-unit RBC transfusions in surgical and obstetrical populations[3-7]. The essential problem of all these studies is that they introduced a considerable selection bias by simply comparing the pretransfusion hemoglobin levels and the transfusion requirements of patients having received one or two RBC units. Not surprisingly, these studies showed that patients with single-unit transfusions had higher or even normal pretransfusion hemoglobin levels when compared to those receiving double-unit transfusions, and for the vast majority of these single-unit transfusions todays guidelines would not have recommended RBC transfusions at all. However, no study has evaluated the effect of double- or single-unit RBC transfusion in patients with hyporegenerative anemia with comparable pretransfusion hemoglobin levels and there is no evidence supporting double-unit RBC transfusions in patients without active bleeding.

A restrictive transfusion policy with stringent transfusion triggers and a cautious use of blood products is the single most effective measure to reduce transfusion requirements and given the scarcity and inherent risks of allogeneic blood products a reduction of blood transfusions is of major health and economic interest. Reducing the volume per transfusion may save a considerable number of RBC units thereby reducing the patients' exposure to allogeneic blood products[8]. However, despite a lack of studies, most guidelines recommend double-unit transfusions, while only few more recent guidelines allow single-unit RBC transfusions in the absence of

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active bleeding[9-14]. Nonetheless, surveys on transfusion practices have shown that more than 90% of the physicians currently transfuse two RBC units simultaneously showing that they have not yet implemented this new transfusion policy[15-18].

Since data suggest that single-unit transfusions may considerably reduce the total RBC requirements we changed our policy for hospitalized patients without active bleeding from double- to single-unit RBC transfusions. The current study analyzed the effect of the new RBC transfusion policy with regards to the overall RBC requirements and the transfusion efficiency, the adherence to the transfusion policy, as well as safety aspects including the bleeding risk and the number of transfused platelets.

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## Design and Methods

*Study population and protocol*

This single-center study was performed in the leukemia and the hematopoietic stem cell transplantation units of the University Hospital Zurich. Patients were eligible if they were older or equal to 16 years, received intensive chemotherapy, autologous or allogeneic hematopoietic stem cell transplantation for hematological malignancies and were treated as inpatients. Patients with AML were treated according to the HOVON 42 protocol and patients with acute promyelocytic leukemia according to the APL 2000 study[19, 20]. Allogeneic hematopoietic stem cell transplantation was performed in a laminar flow unit using standard myeloablative- and non-myeloablative conditioning regimens. Patients receiving chemotherapies predominantly as outpatients were excluded from the study. The local ethical committee approved the study and waived the requirement for written informed consent due to the retrospective nature of the study.

In 2008 we changed our RBC transfusion policy by dispensing only one RBC unit at the time from the blood bank. The single-unit transfusion policy was established in all hospital wards with the exception of the intensive care units, the emergency wards and the operating rooms. More than one RBC unit was dispensed only if explicitly prescribed by the treating physician (e.g. in cases with active bleeding). To evaluate the effect of the new transfusion policy, we performed a retrospective single-center analysis from July 2007 to December 2009 comparing two cohorts of patients receiving either double- or single-unit RBC transfusions. We restricted the analysis to patients with hematological malignancies receiving intensive chemotherapies or hematopoietic stem cell transplantation, as the transfusion requirements in these patients are high and the transfusion triggers predictable. In

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order to avoid a selection bias, the analysis also included all transfusions given in the intensive care units, emergency wards and operation rooms unless stated otherwise.

*Transfusion policies*

All patients had daily white blood cell and platelet counts, hemoglobin, and hematocrit determinations. The RBC transfusion trigger was a morning hemoglobin level ≤60g/L or the presence of anemia symptoms such as fatigue, resting dyspnea, and dizziness. All RBC units were leukocyte-reduced by means of filtration before storage. The maximally tolerated leukocyte count after filtration was $<1x10^6$ leukocytes/unit. The volume of the RBC units ranged from 200 to 350mL and the maximal age of RBC was 42 days according to the Swiss legislation. RBC units were generally not irradiated, but all patients with autologous or allogeneic HSCT or chemotherapies with purine analogues received exclusively cellular blood products that were irradiated with 25 Gy.

Platelets were transfused as previously described[21]. All platelet units were leukocyte-reduced by means of filtration before storage and contained $\geq 2.5x10^{11}$ platelets. All patients with morning platelet counts $\leq 5x10^9$/L received prophylactic platelet transfusions irrespective of bleeding signs. In case of fever or during HSCT, the platelet transfusion trigger was $\leq 10x10^9$/L. There was no change of the platelet transfusion policy in the two periods.

*Measurements and definitions*

We analyzed the reduction in the total number of RBC units per therapy cycle and per day of aplasia as well as determinants related to transfusion efficiency and safety, i.e. the number of platelet transfusions, bleeding incidence, outpatient RBC transfusions, the overall survival and adherence to transfusion policy.

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The hemoglobin increment was determined by subtracting the morning hemoglobin value one day after the transfusion from the one directly before transfusion. Therapy cycles lasted from the first day of chemotherapy or the day of HSCT until neutrophil recovery (absolute neutrophil count (ANC) > $0.5x10^9$/L for 3 consecutive days). The time until RBC recovery lasted from the first day of chemotherapy or the day of HSCT until the reticulocytes increased to > 1%. The duration of aplasia time was from the first day when ANC were ≤ $0.5x10^9$/L until ANC recovery. Major bleeding episodes requiring RBC transfusions or non-elective interventions were analyzed from the patient charts. Due to the retrospective assessment, minor bleedings could not be reliably assessed and were not evaluated in this study. The adherence to the transfusion policy was displayed as the percentage of transfusions given as single-unit or double-unit in the respective transfusion periods. Risk assessment for AML was made according to the HOVON risk score, for patients with ALL according to the GRAALL 2005 study. Patients receiving allogeneic transplantation other than in first complete remission or in first chronic phase for CML were considered as poor risk as well as all patients receiving HSCT for other malignancies.

*Statistical analysis*

Baseline characteristics are displayed as proportions or medians with interquartile ranges (IQR). Patients with double- and single-unit RBC transfusions were compared using Mann-Whitney-U test for continuous variables or chi-squared test for categorical data, as appropriate. To evaluate the independent association between the transfusion policy and the number of RBC units/therapy we applied multiple linear regression modelling. We controlled for the aplasia time during a therapy cycle as important determinant for the total requirement of RBC units and

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other potential confounders such as patients' age at diagnosis, and hemoglobin levels prior to transfusion and the proportion of irradiated RBC units. The model was further adjusted for the clustering of the data (i.e. repeated procedures in the same patients) by applying robust standard errors[22].

The overall survival was calculated from the beginning of the chemotherapy or the day of HSCT until death or last follow-up. The survival observation of patients receiving more than one therapy cycle was censored at the beginning of the next cycle. Survival differences between the two transfusion policy groups were estimated with the method of Kaplan and Meier and compared by log rank test as well as by using multivariate stepwise Cox regression analysis further controlling for potential confounders. All reported p-values are two-sided, and $p<0.05$ were assumed to be statistically significant.

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## Results

*Baseline characteristics*

The study comprised 139 patients receiving 272 therapy cycles. Baseline characteristics are shown in table 1. They were equally distributed among the patients in the single- and double-unit period. The median age of the study population was 49 years (IQR 37-58), 72 (52%) of the patients were male and 67 (48%) female. The majority of the patients were treated for acute myelogenous leukemia (AML, 102, 73%), acute lymphoblastic leukemia (ALL, 17, 12%) or Hodgkin and non-Hodgkin lymphoma (12, 9%). Intensive chemotherapy consisted of induction (136, 50%), consolidation (35, 13%) and reinduction (16, 6%). The remaining therapies were allogeneic (81, 30%) or autologous HSCT (4, 1%). The median time from start of the chemotherapy or from HSCT until neutrophil recovery was 23 days (IQR: 20-28) and the median aplasia time 17 days (IQR: 12-23). The median time until reticulocyte recovery was 27 days (IQR: 24-34).

*RBC transfusions*

Table 2 displays the results of the RBC transfusions in more details. A total of 2212 RBC units were given in 1548 transfusions. During the double-unit period 1242 (56%) RBC units were transfused in 134 (49%) therapy cycles and during the single-unit period 970 (44%) RBC units were transfused in 138 (51%) cycles. Ninety-six percent of the RBC transfusions were ABO identical and 4% ABO compatible. During the study period, only one severe transfusion reaction was reported (transfusion-associated volume overload, 1/1548, 0.064%). The median number of RBC units transfused per therapy cycle was 7 (IQR: 4-11) with patients undergoing conventional intensive chemotherapy requiring significantly more RBC units (8, IQR: 5-12) as compared to HSCT (4, IQR: 2-8; $p<0.001$). However, there was no significant

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difference in the RBC transfusion requirements between chemotherapy and HSCT when analyzed per aplasia day (p=0.832). The median number of transfused RBC per aplasia day was 0.38 units (IQR, 0.25-0.63).

During one transfusion the median number of RBC units administered was 2 (IQR: 1-2) in the double- and 1 (IQR: 1-2) in the single-unit period (p<0.001). To avoid a selection bias, this analysis also included all transfusions given to patients in the intensive care unit and the operation room (n=133, 9%), while there were no transfusions in the emergency ward. However, as shown in Table 2, exclusion of RBC units given in the ICU setting did not significantly change the results.

During 20 therapy cycles no RBC units were transfused at all. Eight cycles without RBC transfusion support were administered during the double- and 12 during the single-unit period. Fifteen of these therapy cycles were allogeneic HSCT with reduced-intensity (7) or myeloablative conditioning (8). The median aplasia time in this group was 8 days (IQR 5-12). The remaining five therapy cycles were consolidation chemotherapies for AML with a median aplasia time of 9 days (IQR 7-12). The aplasia time was significantly shorter in therapy cycles without transfusions as compared to those with transfusions (median 8 vs. 20 days, p<0.001).

*The effect of the single-unit RBC transfusion policy*

As shown in figure 1, the change of the transfusion policy led to a 25% reduction of the transfused RBC units per therapy cycle (double-unit: median 8, IQR 4-13; single-unit: median 6, IQR 3-10; p=0.003). Normalization of the transfusion requirements to one aplasia day resulted in a 24% reduction of the RBC transfusions in the single-unit period. During the double-unit period, a median of 0.46 RBC (IQR: 0.30-0.72) units were transfused per aplasia day, while a median of 0.35 (IQR: 0.20-0.50) RBC units were transfused during the single-unit period (p<0.001).

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Even though the median RBC transfusions per aplasia day were less in the single unit period, the time between transfusions was also less in the single unit period. Although there was no difference in the median number of days between the two groups, the mean time between transfusions was significantly shorter in the single-unit period (3.25 vs. 4.05 days, $p<0.001$). The difference between the two groups was approximately 20% indicating that the change to a single-unit transfusion policy moderately increases the workload for the hospital health care employees.

Patients during single-unit period had slightly lower hemoglobin levels at the time of discharge (74 g/L vs. 78 g/L, $p<0.001$), whilst there was no difference at the beginning of the therapy (89 vs. 89 g/L). However, the lower hemoglobin levels at the time of discharge did not translate into a higher RBC transfusion requirements as outpatients (Double-unit: median 0 (IQR: 0-1, range: 0-21) RBC units; single-unit: median 0 (0-0, range: 0-45) RBC units, $p=0.819$). Likewise, the time until RBC recovery was similar in the two groups.

The effect of the transfusion policy was further confirmed in a linear regression model adjusting for confounding factors and clustering of multiple transfusions in the same patient. The change from double- to single-unit transfusion policy remained independently associated with a significant reduction of 2.7 units (95%-CI -4.3;-1.1, $p=0.001$) per therapy cycle (table 3). As expected, increasing aplasia time was associated with higher RBC transfusion requirements, while the gender and age of the recipients, irradiation of the RBC as well as the haemoglobin levels prior to transfusion did not influence the transfusion requirements.

*Adherence to the single-unit RBC transfusion policy*

Adherence to the assigned RBC transfusion strategy was analyzed by calculating the percentage of correctly administered RBC transfusions in the two

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study periods (Figure 2). Single units were transfused in 25% of the cases during the double- and in 84% during the single-unit period. In 130 transfusions (16%) during the single-unit period two or more RBC units were administered consecutively. The reason for the non-adherence to the single-unit transfusion policy was evaluable in 63% of the cases. Lack of knowledge of the new transfusion policy (21%), hospitalization in the ICU (15%), bleeding events (13%), low hemoglobin values (11%), or transfusions before discharge (3%) were the major reasons for breaking the transfusion policy. Lack of knowledge was primarily seen within the first 4 months after changing the transfusion policy or if new physicians prescribed RBC transfusions. In the remaining 37% of the transfusions there was no clear indication for the non-adherence of the transfusion policy.

*RBC transfusion triggers*

The RBC transfusion trigger in hospitalized patients was ≤ 60g/L in the absence of anemia symptoms during both periods. A total of 567 (37%) RBC transfusions were given in patients with morning hemoglobin levels lower or equal to 60g/L, 778 (51%) with 61-70g/L, 164 (11%) with 71-80g/L, and 19 (1%) with hemoglobin levels >80g/L. During the single-unit period, significantly more transfusions were administered in patients with hemoglobin values lower or equal to 60gl/L (26% vs. 47%, $p<0.001$), while more patients received RBC transfusions with hemoglobin levels between 61-80g/L during the double unit period (74% vs. 53%). This also resulted in a significantly lower hemoglobin level at the time of RBC transfusions during the single-unit period (median 61 (IQR, 58-65) g/L as compared to the double-unit period (median 64, (IQR: 60-69) g/L ($p<0.001$).

*Safety of single-unit RBC transfusions*

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The lower hemoglobin levels may result in a higher bleeding risk due to altered rheological properties in severely anemic patients. To exclude this, we analyzed the bleeding episodes in the two cohorts and the total number of transfused platelets. Severe bleedings occurred in 18 therapy cycles. During these cycles 213 RBC units were administered which equals 14% of the total RBC units. There was no significant difference in the number of therapy cycles with severe bleeding episodes in the double-unit period (7, 5.2%) and single-unit period (11, 8.0%, p=0.362) and the median number of platelets transfused per therapy cycle was 5 (2-9) and 5 (3-9) in the double- and single-unit period (0.896).

Finally, as shown in figure 3, we evaluated the overall survival as a measure for safety after chemotherapy and HSCT. Patients receiving more than one therapy cycle were censored at the time of the next cycle. The median observation time was 78 (9-1087) days. The 30- and 100-day survival probability was 98% (95%-confidence interval 96-99%) and 89% (84-94%) without differences between the two groups (p=0.893) indicating that the transfusion policy had no influence on the overall survival.

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## Discussion

Our retrospective cohort study demonstrates for the first time that a change from double- to single-unit RBC transfusion policy is safe and associated with a reduction of 25% of RBC transfusion requirements in a population with hemato-oncological disorders. This finding demonstrates that the long-standing dogma that two RBC units are necessary for an adequate hemoglobin increase has to be critically revised.

Although each year over 75 million units of blood are transfused worldwide, both the optimal number of RBC units per transfusion and the best RBC transfusion trigger remain controversial[11]. As a consequence, physicians have to rely primarily on clinical experience rather than published data for their decision-making. In the last decades, the general recommendation was to give two RBC units simultaneously, while single-unit RBC transfusions were discredited as useless[1-3] and some authors even suggested to critically revise the local transfusion program if more than 50% of the RBC transfusions were given as single-units[23].

However, this was mainly based on few studies specifically analyzing the effect of single-unit transfusions. The main findings of these studies were that in surgical or obstetric units approximately 25% of all transfusions were single-units. However, over 50% of all patients received single-unit transfusions at hemoglobin levels >100g/L and approximately 80% of all transfusions were judged to be questionable or not indicated[5-7]. The studies share several limitations: i) they were performed several decades ago, when the transfusion practices as well as the blood products considerably differed from today's transfusion technologies. ii) All studies analyzed single-unit RBC transfusion by comparing patients having received one or two RBC units without clear transfusion guidelines. In the vast majority of patients receiving only one RBC unit the transfusions were indeed not indicated because the

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pretransfusion hemoglobin values were close to normal. iii) None of the studies analyzed single-unit RBC transfusions in a non-surgical population.

In contrast, a single-center analysis found that almost 50% of all transfusions were given as single-units, 62% of which were indicated[24]. They concluded that it would be an error to give two units, if one unit is sufficient to correct anemia. One more recent study theoretically analyzed the effect of transfusing only one RBC unit at the time concluding that a single-unit RBC transfusion strategy has a considerable potential to save RBC units and that this was more pronounced when applying lower transfusion triggers[8]. Our current study analyzed for the first time two cohorts of patients who were subjected to either transfusion policy, thus avoiding the selection bias of earlier studies. The limitations of the study are the retrospective single-center analysis, the lack of standardized bleeding assessments and the lack of a quality of life assessment of the patients during the therapy.

Some studies have suggested that a lower hematocrit in the peripheral blood is associated with a poorer marginalization of the circulating platelets and consequently with an increased bleeding risk[15]. Thus, one major concern at the time of changing the transfusion policy in our institution was an increased risk for major bleedings and higher platelet transfusion requirements. Our data, however, reveal no evidence for higher bleeding rates or higher platelet requirements in the single-unit transfusion group.

Moreover, some concerned the higher workload for the health care professionals due to a more frequent transport of RBC units from the local blood bank. It is difficult to assess the exact costs of this blood transport. Indeed, the time between two RBC transfusions was approximately 20% shorter during the single-unit period leading to a higher transfusion frequency and potentially to a higher workload of the health care professionals. However, it is not clear whether the reduced

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workload due to fewer transfusions outweighs the workload of the blood transport. And even if the workload is moderately increased, we believe that the higher workload is justified given the inherent risk of each blood transfusion and the hospital logistics for blood supply should be improved rather than giving unnecessary blood transfusions to patients.

As for the workload, it is difficult to provide exact data on the real costs of transfusions of blood products. A recently published study meticulously analyzed the real costs of RBC transfusion in four hospitals[25]. In this study, an activity-based costing model was constructed taking into considerations tasks and resource consumption (materials, labor, third-party services, capital) related to blood administration. The median costs of one RBC transfusion in surgical patients were $760.82± 293.74. In the current study, each patient received a median of 15 RBC units during the whole treatment resulting in a total amount $11412 for RBC transfusions. Thus, a 25% reduction leads to savings of $2853 per patient.

The best transfusion trigger is a long-standing matter of debate. It is generally acknowledged that patients should receive RBC transfusions if the hemoglobin is lower or equal to 60g/L[26, 27]. A number of studies have analyzed transfusion triggers in ICU and recently in cardiac surgery patients showing that a restrictive transfusion policy resulted in a significant reduction of the transfusion requirements with comparable or even superior mortality rates[28-33]. A meta-analysis indicated that the use of a restrictive transfusion trigger resulted in an average saving of 0.93 units of red cells per transfused patient[26]. In patients with hemato-oncological disorders only limited data exist regarding the optimal transfusion threshold[34]. In patients receiving intensive chemotherapies for AML the requirements differed considerably between centers and a more restrictive transfusion threshold seems to be feasible in these patients[35, 36].

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An interesting finding of our study shows that the hemoglobin levels directly before transfusion of RBC were slightly lower during the single unit period despite similar transfusion guidelines in the two periods. Likewise, the hemoglobin levels at the time of discharge were slightly lower, but this difference did not translate into a higher transfusion rate as outpatients. These findings may indicate that anemia during transfusion dependency is better tolerated in the absence of large fluctuations between the peak and trough hemoglobin caused by the administration of 2 RBC units. In the situation of fewer clinical symptoms the patients may also better tolerate the lower transfusion threshold. It seems rather unlikely that more patients suffered from fatigue and anemia symptoms during the single-unit period, since these symptoms were considered as transfusion triggers throughout the study duration. However, we did not perform a proper assessment of the fatigue and the quality of life and therefore we cannot draw definite conclusions.

In conclusion, this is the first study indicating that a change to a single-unit transfusion policy can safely reduce the RBC transfusion requirements by approximately 25% without changing the transfusion triggers. Our data suggest that a single-unit RBC transfusion policy is effective and cost saving and is not associated with an increased risk for the patients, but with a moderately elevated workload for the health care professionals. Given the scarceness of allogeneic blood products and the inherent risk of all blood transfusions, these results may have a major impact in the transfusion strategies for patients with hyporegenerative anemias. These data have to be confirmed in prospective randomized trials.

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## Authorship contributions

MDB, BG, GS, and US designed the study. MDB, BG and KA collected the data. GS and OS performed the statistical analysis. MDB and GS wrote the manuscript. All authors critically reviewed the manuscript and approved its final version.

## Disclosures

The authors have no conflicts of interest to declare.

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## Tables

### Table 1. Baseline Characteristics.

| | Transfusion strategy | | |
|---|---|---|---|
| | **Double** | **Single** | **P value** |
| **Patients*** | 77 (55) | 62 (45) | |
| **Cycles** | 134 (49) | 138 (51) | |
| **Age$** | 51 (41-58) | 47 (33-56) | 0.126 |
| **Gender** | | | 0.470 |
| Male | 42 (54) | 30 (48) | |
| Female | 35 (46) | 32 (52) | |
| **Disease** | | | 0.123 |
| AML | 56 (73) | 46 (74) | |
| ALL | 6 (8) | 11 (18) | |
| Lymphoma | 8 (10) | 4 (6) | |
| Others | 7 (9) | 1 (2) | |
| **Disease stage** | | | 0.450 |
| Good | 28 (21) | 37 (27) | |
| Intermediate | 33 (25) | 35 (25) | |
| Poor | 73 (54) | 66 (48) | |
| **Therapy** | | | 0.559 |
| Induction | 67 (50) | 69 (50) | |
| Consolidation | 15 (11) | 20 (15) | |
| Reinduction | 6 (5) | 10 (7) | |
| Allogeneic HSCT | 43 (32) | 38 (27) | |
| Autologous HSCT | 3 (2) | 1 (1) | |
| **Duration of therapies$** | | | |
| Time of aplasia | 17 (12-22) | 18 (12-23) | 0.358 |
| CT until end of aplasia | 23 (20-27) | 23 (20-28) | 0.599 |
| CT until reticulocytes >1% | 29 (23-35) | 27 (24-32) | 0.082 |

*Statistics are number and percentages unless otherwise indicated
$ Median (Interquartile range)
AML, acute myelogenous leukemia; ALL, acute lymphoblastic leukemia; CT, Chemotherapy; HSCT, hematopoietic stem cell transplantation

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**Table 2. RBC transfusions.**

| | Transfusion strategy | | |
|---|---|---|---|
| | **Double** | **Single** | **P value** |
| **Administered RBC units*** | | | |
| Total | 1242 (56) | 970 (44) | |
| Chemotherapy | 922 (54) | 791 (46) | |
| HSCT | 320 (64) | 179 (36) | |
| **RBC units/transfusion** | | | <0.001 |
| Mean (SD) | 1.76 (0.49) | 1.18 (0.47) | |
| Median (IQR) | 2 (1-2) | 1 (1-1) | |
| **RBC units/transfusion, excluding ICU transfusions** | | | <0.001 |
| Mean (SD) | 1.79 (0.42) | 1.14 (0.38) | |
| Median (range) | 2 (2-2) | 1 (1-1) | |
| **RBC units/transfusion, excluding severe bleedings** | | | <0.001 |
| Mean (SD) | 1.79 (0.43) | 1.15 (0.385) | |
| Median (range) | 2 (2-2) | 1 (1-1) | |
| **Transfusion trigger (g/L)** | | | <0.001 |
| ≤60 | 181 (26) | 386 (47) | |
| 61-70 | 406 (57) | 372 (45) | |
| 71-80 | 107 (15) | 57 (7) | |
| >80 | 12 (2) | 7 (1) | |
| Median (IQR) | 64 (60-69) | 61 (58-65) | <0.001 |
| **Hb increase/transfusion**$ | 12 (6-17) | 7 (4-11) | <0.001 |
| **Hb prior to therapy and at discharge**$ | | | |
| Prior | 89 (78-104) | 89 (74-109) | 0.992 |
| At discharge | 78 (72-85) | 74 (67-80) | <0.001 |
| **Irradiation** | | | <0.001 |
| No | 342 (48) | 547 (66) | |
| Yes | 364 (52) | 275 (34) | |

*Statistics are numbers (percentage) unless otherwise indicated
$Median (Interquartile range)
Hb, hemoglobin; HSCT, hematopoietic stem cell transplantation; IQR, interquartile range; SD, standard deviation; RBC, red blood cells

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**Table 3. Multivariate linear regression analysis.**

| | Units/therapy cycle | 95%-CI | P value |
|---|---|---|---|
| **Transfusion policy** | -2.7 | -4.2;-1.2 | 0.001 |
| **Aplasia time** | 0.3 | 0.2; 0.4 | <0.001 |
| **Gender** | -1.2 | -2.6; 0.2 | 0.100 |
| **Age at diagnosis** | 0 | 0.0; 0.1 | 0.225 |
| **Irradiation of RBC** | -0.8 | -2.4; 0.7 | 0.294 |
| **Hb prior to transfusion** | 0.1 | -0.1; 0.3 | 0.255 |

Dependent variable: Cumulative units per therapy cycle

Hb, hemoglobin; RBC, red blood cells

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## Figure legends

**Figure 1. Reduction of RBC units per therapy and transfusion-free time.**

The boxplots display medians, interquartile ranges, and 95% confidence intervals. The double RBC-unit period is displayed in light grey and the single-unit period in dark grey. **A** Changing of the transfusion policy led to a 25% reduction of the transfused RBC units per therapy cycle (p=0.003). **B** Normalization to one aplasia day resulted in a 24% reduction of the RBC transfusions in the single-unit period (p<0.001). **C** The mean time between two transfusions was 20% longer in the double-unit period (p<0.001).

**Figure 2. Adherence to the transfusion policy.**

Adherence to the assigned RBC transfusion strategy was analyzed by calculating the percentage of correctly administered RBC transfusions in the two study periods. Light grey indicates 1 RBC unit, dark grey 2, and black >2 RBC units per transfusion. Single units were transfused in 25% of the cases during the double- and in 84% during the single-unit period.

**Figure 3. Overall survival according to the RBC transfusion policy.**

Kaplan-Meier survival estimates in patients during the double- and single-unit RBC period. The 30- and 100-day survival probability was 98% (95%-confidence interval 96-99%) and 89% (84-94%) without differences between the two groups (p=0.893) indicating that the transfusion policy had no influence on the overall survival.

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**Figure 1. Reduction of RBC units per therapy and transfusion-free time.**

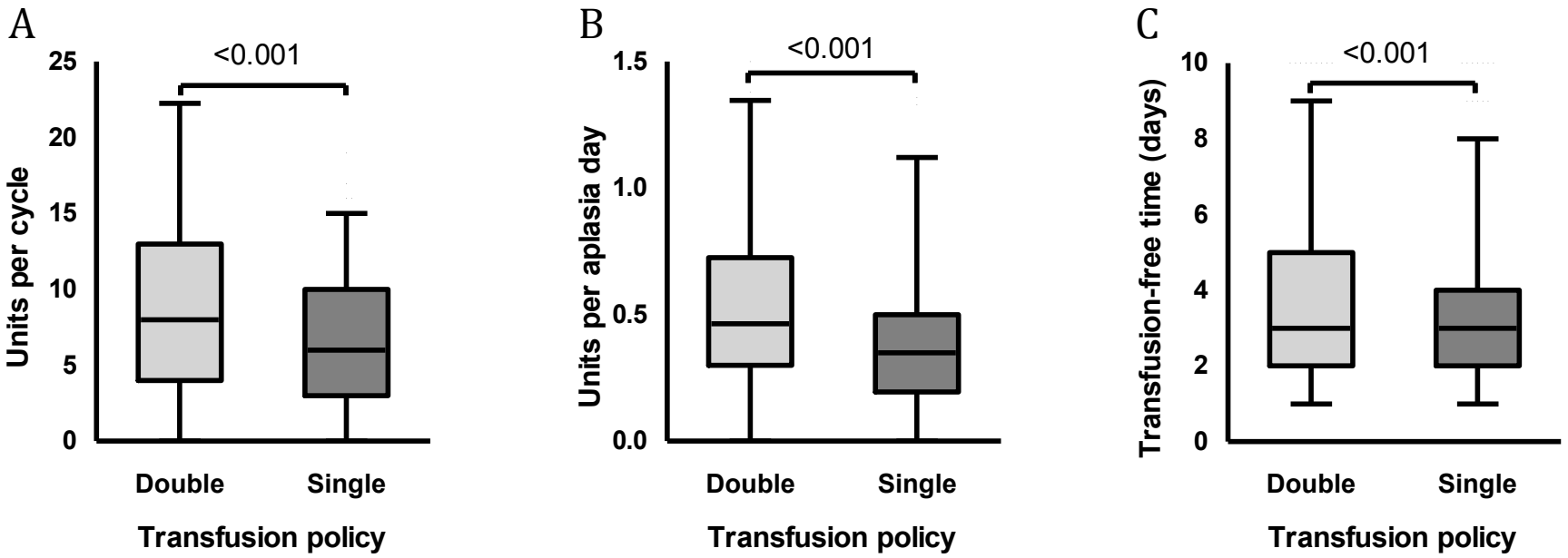

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**Figure 2. Adherence to the transfusion policy.**

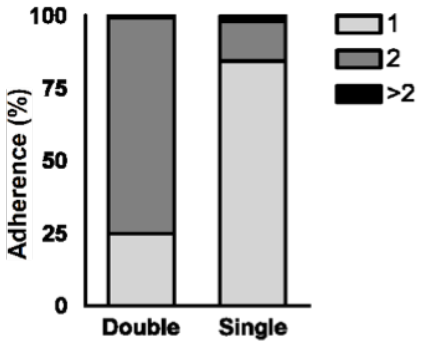

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**Figure 3. Overall survival according to the RBC transfusion policy.**